

PART 2K

Hepatitis A, B, and C

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Hepatitis A, B, and C cause acute infection of the liver that may manifest as an acute icteric illness or be detected incidentally as raised transaminase levels.¹ Most cases are diagnosed only in retrospect on serological screening. Hepatitis B and C can persist as chronic infections (>6 months).

Hepatitis A

Hepatitis A virus (HAV) is transmitted faeco-orally.^{2–3} There is evidence for sexual transmission between homosexual men with several outbreaks reported. The specific risk factors are not well defined but probably relate to oro-anal or digital-rectal contact,^{1–4–5} particularly in settings such as public saunas and dark rooms. Acute icteric hepatitis appears after an incubation period of 15–45 days, symptoms last for about 6 weeks, and it is only rarely fatal. Most infections are asymptomatic (but severity increases with age). Infectivity lasts from approximately 2 weeks before the onset of jaundice to 1 week after.⁶

Diagnostic tests for HAV are recommended in anyone presenting with an acute illness or raised transaminase levels, suggesting acute hepatitis, and in contacts of known cases (sexual, household, or other close contact) (evidence level II).

Screening of asymptomatic sexually transmitted diseases (STD) clinic attendees is recommended to ascertain their immune status only if they meet the criteria for hepatitis A vaccination (see National Guideline on Management of the Viral Hepatitis A, B and C), which includes homosexual men in regions where an outbreak of hepatitis A has been reported, injecting drug users, and patients with chronic hepatitis B or C or other causes of chronic liver disease (evidence level III).^{1–6}

Hepatitis B

Hepatitis B virus (HBV) infection is transmitted vertically (mother to child), parenterally, and sexually.^{7–14} There is a much lower risk to household contacts of acute cases and high infectivity carriers. Of individuals seen in STD clinics, those at greatest risk of infection are homosexual men and injecting drug users.^{7–15} Acute hepatitis B has an incubation period of 40–160 days with symptoms lasting up to 12 weeks. Fulminant hepatitis occurs in about 1% and may be fatal.⁶ About 5% of infected adults are asymptomatic.^{6–16} About 5–10% of immunocompetent patients and up to 40% of immunocompromised patients develop chronic infection. Symptomatic acute infection very rarely leads to chronicity. Infectivity lasts from approximately 2 weeks before the onset of jaundice until the loss of infection markers. Cirrhosis or liver cancer may develop in up to 20% of chronic carriers over 10–50 years.^{16–17} Tests for HBV markers are indicated for diagnostic purposes and for screening. Screening serves the dual purpose of identifying those who are currently infected, and those who are immune by natural infection (and by elimination those who are still susceptible and should receive vaccine).

Diagnostic tests for HBV are recommended in anyone presenting with suspected acute hepatitis and in those with

symptoms or signs of chronic liver disease, or abnormal LFTs consistent with acute or chronic hepatitis (evidence level II).

Screening of asymptomatic STD clinic attendees is recommended if they fall into one of the groups at increased risk of hepatitis B and who should be given vaccine if still susceptible. The testing strategy used should identify both those who are already immune to infection and those who are currently infected (most will be chronic carriers). Those who should be screened include homosexual men or their contacts, sex workers or their contacts, injecting drug users or their contacts, recipients of blood/blood products, needle-stick recipients, sexual assault victims, HIV positive people and sexual partners of HBsAg positive people (evidence level II).^{7–15} and people from areas where hepatitis B is endemic.

Screening of patients who have been born, raised, or otherwise resident in endemic countries and travellers who have had sexual contacts in endemic countries, is also recommended to identify those who are currently infected and may be at risk of transmitting infection to others (those who are still susceptible should be given vaccine only if they are at future risk of infection) (evidence level II).

Hepatitis C

Hepatitis C virus (HCV) is transmitted parenterally although there is a low rate of sexual and vertical transmission, which is more likely to occur within the setting of HIV/HCV co-infection.^{14–18–22} Acute icteric hepatitis is rare (about 10% of infections). The majority (60–70%) develop chronic infection. As with HBV infection, cirrhosis and liver cancer ensue in 20% or more over the next 10–50 years.^{23–24}

Diagnostic tests for HCV are recommended in anyone presenting with suspected acute hepatitis, and in those with symptoms or signs of chronic liver disease, or abnormal liver function tests (LFTs) consistent with acute or chronic hepatitis (evidence level II).

Screening of asymptomatic STD clinic attendees is recommended if they fall into one of the groups at increased risk which includes injecting drug users, recipients of blood/blood products, needlestick recipients, HIV positive people, and sexual partners of HCV positive people (evidence level II).^{14,18–24}

RECOMMENDED TESTS

Note: For simplicity the following recommendations refer to tests, such as the enzyme linked immunosorbent assay (ELISA) or DNA amplification that are all, unless otherwise stated, conducted on blood samples. Most commercial serological assays for hepatitis virus infections can be used with either serum or plasma. Local protocols should be agreed with relevant laboratory departments.

Abbreviations: ELISA, enzyme linked immunosorbent assay; HAV, hepatitis A virus; HBeAg, hepatitis B “e” antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; LFTs, liver function tests; RIBA, recombinant immunoblot assay; RT-PCR, reverse transcriptase-polymerase chain reaction; STD, sexually transmitted diseases

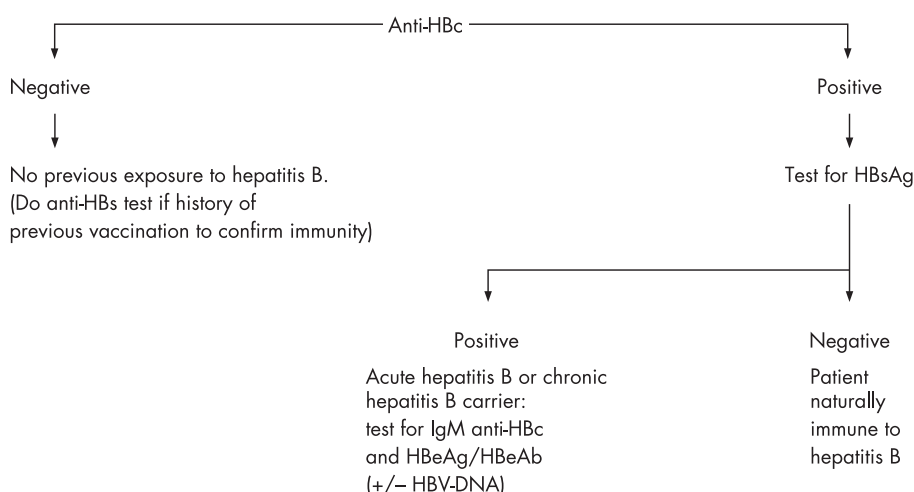


Figure 1 Flow chart for hepatitis B screening using anti-HBc as the primary screening test.

Hepatitis A

To diagnose suspected acute hepatitis: ELISA for anti-HAV IgM (detectable at or before the onset of symptoms and persists for up to 6 months) (evidence level II).²⁵⁻²⁷

To determine if immune to infection: ELISA for anti-HAV (total antibody—standard tests detect both IgM and IgG antibody) (evidence level II).²⁵

Sensitivities and specificities approach 100% (evidence level II).²⁷⁻²⁹

Assays for salivary samples exist but are not generally available for routine use. They have a sensitivity of about 80% for IgA (evidence level II).³⁰

Hepatitis B

To diagnose suspected acute hepatitis: ELISA for hepatitis B surface antigen (HBsAg) and IgM anti-HBc antibody. If HBsAg positive, proceed to hepatitis B “e” antigen (HBeAg) and antibody (HBeAb) (evidence level II).^{28 31-34}

Screening in asymptomatic patients may include tests for HBsAg, anti-HBc, and anti-HBs on all samples, or may follow a sequential testing algorithm (evidence level II). (Figs 1 and 2 show algorithms starting with anti-HBc or HBsAg.^{28 31-34})

Testing for anti-HBs alone before vaccination may also be considered, but must be followed by serological investigation of any patient who remains anti-HBs negative post-vaccine, because they may already be HBsAg positive. Testing for anti-HBc antibody and anti-HBs before vaccination may also be considered (evidence level II).

Assays for anti-HBc and HBsAg in saliva samples have been used for surveillance and research purposes but are not

currently available commercially for diagnostic use³⁵ (evidence level II).

Hepatitis C

To diagnose suspected acute hepatitis C: serum anti-HCV by second or third generation ELISA or other immunoassays (for example, chemiluminescence) (evidence level II).

Different strategies exist to confirm a positive result. These include a recombinant immunoblot assay (RIBA), using another ELISA, or proceeding directly to an assay for HCV-RNA (evidence level II).³⁶⁻⁴⁵ Seroconversion for HCV antibody may take 3 months so antibody tests may give negative results when a patient presents with acute hepatitis (evidence level II). Detection of HCV-RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) or another genome amplification assay will establish or exclude the diagnosis at this time (evidence level II).³⁹⁻⁴² HCV-RNA can be detected as early as 2 weeks after infection. An HCV-antigen ELISA can be used to diagnose acute infection in HCV antibody negative cases, but is not as sensitive as genome detection (evidence level II).⁴⁶

HCV-RNA detection should be repeated 6 months after acute hepatitis C to confirm whether the infection has become chronic (evidence level II).

Screening in asymptomatic patients: As for acute infection but test all patients with detectable HCV-antibody for HCV-RNA to confirm persistent viral replication (evidence level II). Antibody negative patients do not require further testing unless recent infection is suspected, or there is a strong suspicion of infection in an immunocompromised patient in

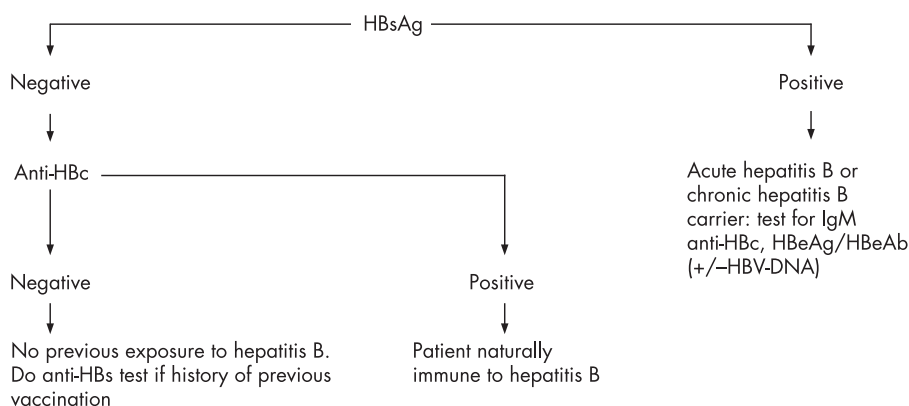


Figure 2 Flow chart for hepatitis B screening using HBsAg as the primary screening test.

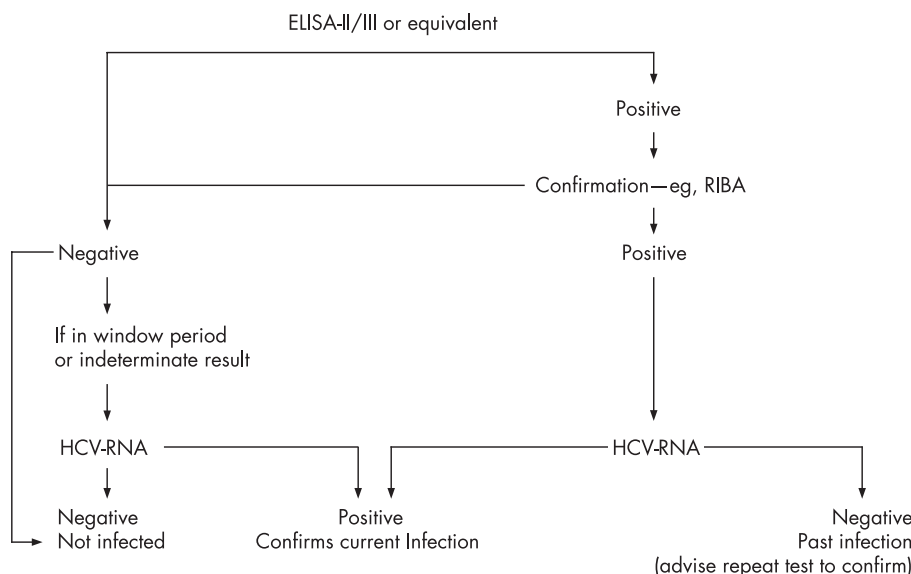


Figure 3 Flow chart for hepatitis C testing using antibody assay.

whom persistent infection has occasionally been reported without detectable antibody (evidence level III).

FACTORS THAT ALTER TESTS RECOMMENDED (SEE FIGS 1–3 ABOVE)

Hepatitis A

Some clinics do not test for anti-HAV in patients who are being considered for vaccination. This may be more cost effective depending upon the age and risk group, but the additional cost may be small if, for example, HAV testing is carried out at the same time as HBV screening (evidence level III).

Hepatitis B

Serum HBV-DNA may be detectable in patients with anti-HBc but without detectable HBsAg.³³ In patients with abnormal LFTs other causes should be excluded before attributing liver disease to HBV infection in such cases (evidence level II). Some patients have detectable anti-HBc but neither anti-HBs nor HBsAg is detectable. These patients should be considered to be immune (evidence level II).

Hepatitis C

In patients with abnormal LFTs serum HCV-RNA may be the only test that is positive during acute HCV infection, or rarely in immunosuppressed patients (see above) (evidence level II).^{36 39 46}

Sexual history

- No change.

Risk groups

- Homosexual men—no change
- Sex workers—no change
- Young patients—no change
- Pregnant women—no change
- Patients who are known contacts—tests as for suspected acute hepatitis.

RECOMMENDATIONS FOR FREQUENCY OF REPEAT TESTING IN AN ASYMPTOMATIC PATIENT

The frequency of testing depends on the history of sexual exposure and number of sexual partners. However, in the

case of hepatitis A and B, once the patient has completed a course of vaccination no further repeat testing is required.

For those at continuing risk and who have not received a course of vaccination, the following is recommended.

Hepatitis A

No routine repeat screening (evidence level IV).

If a previously non-immune homosexual man gives a history of contact with a known case of hepatitis A, post-exposure prophylaxis with vaccine (and possibly immunoglobulin if over 50 years old, immunocompromised, or with co-existing liver disease) should be offered as soon as possible (evidence level II). Prophylaxis needs to be given within 1–2 weeks of exposure, although immunoglobulin may be of additional value for up to 2–3 weeks (evidence level II).^{47–49} Screening for anti-HAV should be offered at the same time as prophylaxis with further tests if indicated clinically (evidence level IV).

Hepatitis B

If a previously non-immune person gives a history of unprotected anal or vaginal sex with a known case of infectious hepatitis B, post-exposure prophylaxis with vaccine should be offered as soon as possible (if less than 6 weeks after exposure) (evidence level II)^{50 51} and screening repeated and again at 3 months after exposure. Hepatitis B specific immunoglobulin should only be given if within 72 hours of first exposure (evidence level II).^{28 31–34}

Otherwise repeat screening at yearly intervals if risk behaviour continues (evidence level IV).^{31 32}

Hepatitis C

The rate of seroconversion after unprotected vaginal or anal sex is about 2% per year if neither partner is HIV positive but the risk rises to over 10% if there is HIV infection in either partner (evidence level II).^{20 21 52 53} Repeat screening should be offered to contacts with an HCV infected partner who continue to be exposed to infection. The optimum frequency has not been defined but may be every 6–12 months (evidence level IV).^{23 24 36 37}

Repeat screening of others considered to be at risk, as listed above, may be offered. No frequency of screening has been defined, but annual testing may be considered (evidence level IV).

There is value in screening at 6 weeks and 12 weeks using an HCV-RNA assay after a high risk incident (for example,

parenteral exposure from an HCV positive source) to detect acute infection early, when therapy may reduce the risk of ensuing chronic infection, at least in HIV uninfected patients^{54–56} (evidence level II). Antibody tests should be repeated at 3, 6, and 12 months (evidence level II).

Patients with high risk exposures to any of these viruses should be informed about the symptoms of acute hepatitis and encouraged to seek advice immediately if these develop.

RECOMMENDATION FOR TEST OF CURE

- Not relevant for these infections.
- Patients with newly diagnosed infection caused by HBV or HCV should have serological markers of infection (HBsAg or HCV-RNA) measured 3 and 6 months later to establish whether the infection has become chronic^{16 17 31 57} (evidence level II).
- Serological follow up after antiviral therapy is beyond the scope of this guideline.

STAKEHOLDER INVOLVEMENT

- British Liver Trust
- SHASTD.

RIGOUR OF DEVELOPMENT

Literature search

For each type of hepatitis, a Medline search was performed for the years 1966–2003 (June) for hepatitis types A and B and 1990–2003 (June) for hepatitis C. From the MeSH terms “hepatitis A”, “hepatitis B”, and “hepatitis C”, the following subheadings were used: Diagnosis, Epidemiology, Etiology, Prevention and Control, Transmission, Virology. Textword searches for “hepatitis A”, hepatitis B”, and “hepatitis C” were combined, as appropriate, with textword searches for “complication”, “diagnosis”, “prevention”, “transmission”, “HIV”.

Cross references to published guidelines

The following published guidelines were reviewed and cross referenced with the recommendations made in this guideline.

- Brook MG. European guideline for the management of hepatitis B and C virus infections. *Int J STD AIDS* 2001;**12**(suppl 3):48–57
- Brook MG. National guideline for the management of the viral hepatitis A, B and C. (BASHH Clinical Effectiveness Group, July 2002) www.mssvd.org.uk/CEG/ceguidelines.htm.
- Cramp M, Rosenberg W. Guidance on the treatment of hepatitis C incorporating the use of pegylated interferons. (British Society of Gastroenterology 2003) www.bsg.org.uk/clinical_prac/guidelines/pegylated.htm.

APPLICABILITY

The guideline includes the routine use of HCV-RNA testing which is not available in all microbiology or virology laboratories; however, all centres have access to these tests through reference laboratories.

AUDITABLE OUTCOME MEASURES

- At least 90% of asymptomatic patients in any of the risk groups listed above for screening should have a HAV test or receive hepatitis A vaccine.
- At least 90% of patients in any of the at-risk groups listed should have a HBV and/or HCV test as appropriate.

- At least 90% of patients with symptoms suggesting acute hepatitis should have anti-HAV-IgM, HBsAg, anti-HBc-IgM, and anti-HCV tests.
- At least 90% of patients with a positive test result for HBsAg or HCV-RNA should have the test repeated.

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